BOOK REVIEW

Mixed Effects Models for the Population Approach: Models, Tasks, Methods, and Tools
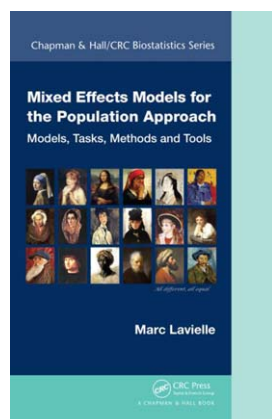
By Marc Laveille

Reviewed by L Aarons[1]

At the end of this review I am required to declare any conflicts of interest and I am going to say none. However, I have known Marc Laveille for some time and had many discussions with him. He describes himself as a statistician specialized in computational statistics and healthcare applications. Consequently, and also knowing him, it was with some trepidation that I opened this book. I expected something very precise and very pedantic and also something very technical. Having read through the book I can report that it is very precise but I was pleasantly surprised at how readable it was and I am speaking as someone who would describe themselves as a PKPD modeler. The hard stuff does come but not until later in the book and in the appendices. The style of the book is to introduce concepts with simple examples gradually building up in complexity.

It is not obvious from the title that the book is closely linked to the Monolix software but this is no great surprise in that the author is also the developer of that software. All of the examples in the book are developed in Monolix and the results come from Monolix runs. Consequently, it will not be immediately obvious to users of other software, such as NONMEM, how to implement the problems. However, it would be wrong to view the book as a Monolix manual. It certainly is useful for that purpose but the user would also need to refer to the Monolix documentation to have full implementation details. The book is also a textbook on nonlinear mixed effects modeling and is a very good addition to the books of Davidian and Giltinan[1] and Bonate.[2] Another issue that is not obvious from the title is that the majority of examples are taken from pharmacokinetics and pharmacodynamics and there is even an appendix on pharmacokinetic modeling. However, the application of the methodology goes far beyond PKPD modeling and it would be unfortunate if practitioners in other disciplines dismissed the book because of this.

The book is divided into four sections: Introduction and Preliminary Concepts, Defining Models, Using Models, and Appendices. The first section is quite philosophical but nevertheless very precise. The point is made several times, often with exclamation marks, that a model is a joint probability distribution of the random variables and this is fundamental to understanding his approach to the subject. Notation is introduced in this section and it is worth spending time getting to grips with it, as it is used consistently throughout the book. In the second section various models are developed, including those related to continuous data and discrete data. In each case the model—structural and statistical—is built up from a simple precursor and additional features are added to demonstrate various extensions to the model. Most of the continuous data models are taken from pharmacokinetics, whereas in terms of discrete data models, examples from count data, categorical data, and time-to-event data are used. Other modeling issues covered include: modeling of joint data (e.g., PKPD models), covariate models, mixture models, hidden Markov models, and stochastic differential equation-based models. Section three contains details of the theory behind the methodology but mainly that related to the SAEM (stochastic approximation of estimation-maximization) algorithm which is used by Monolix. Further results are given in the appendices. It would be necessary for a reader who wanted to understand the finer details of the algorithms to refer to the original literature, although the book provides a good "first look" at this material. As mentioned earlier, the appendices provide various useful material from probability to pharmacokinetics as well as an overview of some of the companion programs to Monolix such as MIxplore for model exploration.

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In summary, I would say the book is an essential companion to the Monolix software but I would highly recommend it to all practitioners of the population approach for the systematic and thorough way it presents the subject.

Conflict of interest: The author declares no conflict of interest.

1. Davidian, M. & Giltinan, D.M. *Nonlinear Models for Repeated Measurement Data* (Chapman & Hall/CRC Monographs on Statistics & Applied Probability, Boca Raton, FL, 1995).
2. Bonate, P.L. *Pharmacokinetic-Pharmacodynamic Modeling and Simulation*, 2nd edn (Springer, New York, 2011).